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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,268	02/16/2001	Jonathan W. Jarvik	2087-010262	5282

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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	PAPER NUMBER
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/788,268	JARVIK, JONATHAN W.	
	Examiner	Art Unit	
	Russell S. Negin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-102* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6 October 2006 has been entered.

Claims 92-102 are examined in this Office action.

Specification

The disclosure is objected to because of the following informalities:

There are drawings embedded in the specification on pages 31 and 33.

These drawings are partially cut off on the right side of the figure.

Page 8 of the specification has the grammatical inconsistency on line 4, "the codons encoding each amino acid [amino acid] in the sequence."

Page 14, line 8 has the units inconsistency, "A 10 ϕl aliquot..."

Page 17, line 7 has the units inconsistency, "A 10 ϕl aliquot..."

Page 41, line 16 has an ending to a sentence with two periods.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 92, 93, 95, 97, and 100-102 are rejected under 35 U.S.C. 102(a) as being anticipated by Blanc et al. [USPAT 5,891,695].

Claims 92, 93, 95, 97, and 100-102 are rejected under 35 U.S.C. 102(e) as being anticipated by Blanc et al. [USPAT 5,891,695].

It should be noted that this application was published as a WIPO document WO94/08014 on April 14, 1994 in French. A translation of this WIPO document is being requested at this time.

Claim 92 states as follows:

A method of analyzing a nucleotide, comprising:

a) providing a polynucleotide having homology to a defined DNA sequence;

b) calculating the masses of two or more polypeptides encoded in two or more reading frames of said defined DNA sequence thereby obtaining a set of predicted mass values;

c) expressing two or more polypeptides from two or more reading frames of said polynucleotide, thereby creating two or more expressed polypeptides;

d) measuring the masses of said two or more expressed polypeptides, thereby obtaining a set of observed mass values; and

e) comparing said set of predicted mass values to said set of observed mass values.

Claim 93 claims a difference in the polynucleotide sequence due to a mutation or polymorphism.

Claim 95 claims use of cDNA as the polynucleotide of interest in claim 92.

Claim 97 claims that the expressed polypeptides are expressed in a living cell.

Claim 100 comprises purification of the polypeptide prior to measuring its measured peptide mass signature.

Claim 101 claims methods of which to accomplish claim 100.

Claim 102 claims spectrometric methods to accomplish claim 92.

The preamble of claim 92 is taught in the abstract of Blanc et al. as "The invention concerns nucleotide sequences coding for a polypeptide."

Step a) in the method is anticipated in Example 1, column 9, lines 30-62 and Example 6, column 39, lines 45-51. Example 1 is entitled, "Isolation of total DNA of *Streptomyces pristinaespiralis* strain SP92." Example 6 contains the text, "it is possible to subclone DNA fragments containing these genes. These subclonings were performed in order to be able to deduce subsequently the nucleic acid sequence of the genes identified,..."

Step c) of the above method is anticipated in Blanc et al. Examples 5.1.1.B and 5.1.2 (columns 14 and 15). In example 5.1.1.B, *S. pristinaespiralis* SP92 Pristinamycin IIA Synthase is purified. The example claims that after this procedure, "the enzyme is pure and, in SDS-PAGE electrophoresis, two subunits of molecular weight estimated at 35,000 and 50,000 are detected." [column 15, lines 20-23] According to Example 5.1.2, polypeptide sequences to be examined, SnaA and SnaB, are cleaved from the protein via Edman degradation, and then purified using high performance liquid chromatography (HPLC). Thus, Example 5.1.2 not only anticipates step c) of the above method, but additionally anticipates claims 100 and 101, which claim "purification of the polypeptide" and "high performance liquid chromatography" as methods for accomplishing this task, respectively.

Steps b), d), and e) are anticipated in Blanc et al., column 46, lines 54-58, and 61-65, which state, "Frames 1 and 3 correspond respectively to the proteins SnaA (SEQ ID NO:17) and SnaB (SEQ ID NO:18) isolated above as described in Example 5 and for which the cloning of the genes is detailed in Example 6... ...Moreover, the molecular masses calculated from the sequences are comparable to the apparent molecular masses of the proteins SnaA and SnaB, estimates, respectively, in SDS-PAGE as described in Example 5." Thus, the polypeptide sequence has its molecular weight measured and calculated with both results being compared. Since Blanc et al. uses gel electrophoresis, Claim 102 is additionally anticipated (Claim 102 dictates methods of measurement of polypeptide masses).

The procedure of claim 92 was accomplished in living cells (i.e. see Example 1 of Blanc et al. in column 9 which shows use of *S. pristinaespiralis*).

Column 47, lines 16-24 reveal that there is a multiple nucleotide insertion in the polynucleotide:

> Comparison of the sequence of the product of open reading frame no. 2 with the protein sequences contained in the Genpro bank reveals that an internal portion of this protein is 36% homologous with an internal portion of the first open reading frame of the insertion sequence (IS891) of Anabaena... This result suggests that open reading frame no. 2, designated ORF 401, belongs to an insertion sequence, and that there is hence an insertion sequence located between the snaA and snaB genes.

Furthermore, this snaA gene is recorded in the sequence listing in column 75 of Blanc et al. as a sequence of cDNA (SEQ ID no:2 in Blanc et al. is snaA).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 92, 98 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blanc et al. in view of Jermutus et al. [Current Opinion in Biotechnology, 1998, volume 9, pages 534-548].

Claim 98 claims expression of the polypeptide in a cell free system.

Claim 99 limits the types of extracts which could be used in the cell free system.

The preamble of claim 92 is taught in the abstract of Blanc et al. as "The invention concerns nucleotide sequences coding for a polypeptide."

Step a) in the method is taught in Example 1, column 9, lines 30-62 and Example 6, column 39, lines 45-51. Example 1 is entitled, "Isolation of total DNA of *Streptomyces pristinaespiralis* strain SP92." Example 6 contains the text, "it is possible to subclone DNA fragments containing these genes. These subclonings were performed in order to be able to deduce subsequently the nucleic acid sequence of the genes identified,..."

Step c) of the above method is taught in Blanc et al. Examples 5.1.1.B and 5.1.2 (columns 14 and 15). In example 5.1.1.B, *S. pristinaespiralis* SP92 Pristinamycin IIA Synthase is purified. The example claims that after this procedure, "the enzyme is pure and, in SDS-PAGE electrophoresis, two subunits of molecular weight estimated at 35,000 and 50,000 are detected." [column 15, lines 20-23] According to Example 5.1.2, polypeptide sequences to be examined, SnaA and SnaB, are cleaved from the protein via Edman degradation, and then purified using high performance liquid chromatography (HPLC). Thus, Example 5.1.2 not only teaches step c) of the above method, but additionally teaches claims 100 and 101, which claim "purification of the polypeptide" and "high performance liquid chromatography" as methods for accomplishing this task, respectively.

Steps b), d), and e) are taught in Blanc et al., column 46, lines 54-58, and 61-65, which state, "Frames 1 and 3 correspond respectively to the proteins SnaA (SEQ ID NO:17) and SnaB (SEQ ID NO:18) isolated above as described in Example 5 and for

which the cloning of the genes is detailed in Example 6... ...Moreover, the molecular masses calculated from the sequences are comparable to the apparent molecular masses of the proteins SnaA and SnaB, estimates, respectively, in SDS-PAGE as described in Example 5." Thus, the polypeptide sequence has its molecular weight measured and calculated with both results being compared. Since Blanc et al. uses gel electrophoresis, Claim 102 is additionally taught (Claim 102 dictates methods of measurement of polypeptide masses).

The procedure of claim 92 was accomplished in living cells (i.e. see Example 1 of Blanc et al. in column 9 which shows use of *S. pristinaespiralis*).

Column 47, lines 16-24 reveal that there is a multiple nucleotide insertion in the polynucleotide:

> Comparison of the sequence of the product of open reading frame no. 2 with the protein sequences contained in the Genpro bank reveals that an internal portion of this protein is 36% homologous with an internal portion of the first open reading frame of the insertion sequence (IS891) of Anabaena... This result suggests that open reading frame no. 2, designated ORF 401, belongs to an insertion sequence, and that there is hence an insertion sequence located between the snaA and snaB genes.

Furthermore, this snaA gene is recorded in the sequence listing in column 75 of Blanc et al. as a sequence of cDNA (SEQ ID no:2 in Blanc et al. is snaA).

However, Blanc et al. does not teach use of cell free systems in peptide expression.

The article of Jermutus et al., entitled, "Recent advances in producing and selecting functional proteins by using cell-free translation," states in the abstract:

> Prokaryotic and eukaryotic in vitro translation systems have recently become the focus of increasing interest for tackling fundamental questions in biochemistry. Cell free systems can now be used to study the in vitro assembly of membrane proteins and viral particles, rapidly produce and analyze protein mutants, and enlarge the genetic code by incorporating unnatural amino

> acids. Using in vitro translation systems, display techniques of great potential have been developed for protein selection and evolution. Furthermore progress has been made to efficiently produce proteins in batch or continuous cell-free translation systems and to elucidate the molecular causes of low yield and find possible solutions for this problem.

Jermutus et al. states in the last paragraph of the second column of page 534, "We will focus primarily on the typical translation systems in use today and discuss some of the factor influencing the amount of total protein made. The most efficient cell-free protein synthesis systems are derived from Escherichia coli, rabbit reticulocytes, or wheat germ..."

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the method of producing the polypeptides involved in the biosynthesis of streptogramins of Blanc et al. in view of the cell-free peptide production method of Jermutus et al., because the cell free system of Jermutus et al. has the advantages listed in the aforementioned abstract (i.e. batch and continuous processing) for more efficient production of proteins.

Claims 92, 94 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blanc et al. in view of Blanc et al. [Journal of Bacteriology, 1995, volume 177, pages 5206-5214] as evidenced by the sequence listing for *Streptomyces pristinaespiralis* in Blanc et al. (1995) number [GenBank Accession Number SPU21215]. This second Blanc et al. reference will be referred to as "Blanc et al. (1995)" throughout this Office action.

Claim 94 claims usage of an exon.

Claim 96 claims usage of an epitope tag.

The preamble of claim 92 is taught in the abstract of Blanc et al. as "The invention concerns nucleotide sequences coding for a polypeptide."

Step a) in the method is taught in Example 1, column 9, lines 30-62 and Example 6, column 39, lines 45-51. Example 1 is entitled, "Isolation of total DNA of *Streptomyces pristinaespiralis* strain SP92." Example 6 contains the text, "it is possible to subclone DNA fragments containing these genes. These subclonings were performed in order to be able to deduce subsequently the nucleic acid sequence of the genes identified,..."

Step c) of the above method is taught in Blanc et al. Examples 5.1.1.B and 5.1.2 (columns 14 and 15). In example 5.1.1.B, *S. pristinaespiralis* SP92 Pristinamycin IIA Synthase is purified. The example claims that after this procedure, "the enzyme is pure and, in SDS-PAGE electrophoresis, two subunits of molecular weight estimated at 35,000 and 50,000 are detected." [column 15, lines 20-23] According to Example 5.1.2, polypeptide sequences to be examined, SnaA and SnaB, are cleaved from the protein via Edman degradation, and then purified using high performance liquid chromatography (HPLC). Thus, Example 5.1.2 not only teaches step c) of the above method, but additionally teaches claims 100 and 101, which claim "purification of the polypeptide" and "high performance liquid chromatography" as methods for accomplishing this task, respectively.

Steps b), d), and e) are taught in Blanc et al., column 46, lines 54-58, and 61-65, which state, "Frames 1 and 3 correspond respectively to the proteins SnaA (SEQ ID NO:17) and SnaB (SEQ ID NO:18) isolated above as described in Example 5 and for

which the cloning of the genes is detailed in Example 6... ...Moreover, the molecular masses calculated from the sequences are comparable to the apparent molecular masses of the proteins SnaA and SnaB, estimates, respectively, in SDS-PAGE as described in Example 5." Thus, the polypeptide sequence has its molecular weight measured and calculated with both results being compared. Since Blanc et al. uses gel electrophoresis, Claim 102 is additionally taught (Claim 102 dictates methods of measurement of polypeptide masses).

The procedure of claim 92 was accomplished in living cells (i.e. see Example 1 of Blanc et al. in column 9 which shows use of *S. pristinaespiralis*).

Column 47, lines 16-24 reveal that there is a multiple nucleotide insertion in the polynucleotide:

> Comparison of the sequence of the product of open reading frame no. 2 with the protein sequences contained in the Genpro bank reveals that an internal portion of this protein is 36% homologous with an internal portion of the first open reading frame of the insertion sequence (IS891) of Anabaena... This result suggests that open reading frame no. 2, designated ORF 401, belongs to an insertion sequence, and that there is hence an insertion sequence located between the snaA and snaB genes.

Furthermore, this snaA gene is recorded in the sequence listing in column 75 of Blanc et al. as a sequence of cDNA (SEQ ID no:2 in Blanc et al. is snaA).

Blanc et al. states in column 3, lines 136, and 25-30:

> The present invention describes in particular the isolation and characterization of the snaA, snaB, snaC, snaD, papA, papM, samS, snbA, snbC, snbD, snbE, and snbR genes. These genes were isolated from a library of genomic DNA of S. pristinaespiralis...
> The snaA, snaB, and samS... genes are present on cosmid pIBV1... The product of the snaA and snaB genes, corresponding to polypeptides SnaA and SnaB, participates in the final step of biosynthesis of the II component of pristinamycins...

Blanc et al. do not state explicit use of exons or epitope tags.

The sequence submission of Blanc et al (1995) (U21215), confirms the linear relationship between the cDNA and genomic DNA of the regions of interest in the bacteria S. pristinaespiralis (i.e. there are no introns in the open reading frames of the genomic DNA). Consequently, snaA is an exon which codes for the protein SnaA.

Blanc et al (1995) also elaborate on the use of antibodies in conjunction with the protein of interest (pristinamycin II synthase or PII_A synthase). An epitope, or region of a protein or antigen that binds to an antibody, is interpreted to be the PII_A synthase. In this case, Figure 5 on page 5213 of Blanc et al. (1995) illustrates using antibody binding in a Western blot and states in the caption, "The Western blot was obtained by using antibodies raised against the two subunits of the PII_A synthase..."

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to modify the use of polypeptides of *Streptomyces pristinaespiralis* to understand biosynthesis of streptogramins in Blanc et al. in view of the study of the structure and function of genes and polypeptides produced from *Steptomyces pristinaespiralis* in Blanc et al. (1995) because Blanc et al. (1995) has more detailed structural information on the biomolecules produced from *Streptomyces pristinaespiralis* which adds further data to the knowledge of methods of biosynthesis of streptogramins in Blanc et al.

Response to Arguments

Applicant's arguments filed 3 August 2006 have been fully considered but they are not persuasive.

Applicant makes several arguments against the anticipatory prior art rejection of Blanc et al.

First the applicant argues that step (a) of instant claim 92 is not taught by Blanc et al. because (as stated in page 5 of the "Remarks" of 3 August 2006), "Example 1 of the '695 patent described the isolation of total genomic DNA from the mycelia of the organism *S. pristinaespiralis*, and does not describe isolation or provision of a polynucleotide with a defined sequence." However, step (a) requires only "providing a polynucleotide having homology to a defined DNA sequence." Step (a) does not require that the polynucleotide sequence be isolated.

Second, applicant argues that step (c) is not taught because (as stated on page 6 of the "Remarks" of 3 August 2006), "The enzyme was not expressed from a polynucleotide having homology to a defined DNA sequence, nor are the two subunit polypeptides of the enzyme encoded in different reading frames of the same DNA sequence—indeed the Example proves that they are expressed from distinct and separate genes..." However, while example 5.1.2 of Blanc et al. shows two independent polypeptides, they are both derived from the oligonucleotide sequence of *S. pristinaespiralis.*

Third, applicant argues that steps b), d), and e) are not taught because the meaning of "frame number" in the reference is inconsistent with the alleged meaning defined by applicant. Applicant claims that frame number (as stated on page 6 of the "Remarks" of 3 August 2006), "as used in the instant application refers to one of the six possible alternative frames in which any DNA sequence might be translated." Yet,

applicant does not point as to a location in the specification of such a defining concept. In examining the specification, the Office cannot find a location for this limiting meaning as well. In the absence of such definition, the meaning of "frame number," such as defined in Table 10 of column 46 of the reference (Blanc et al.) is used to interpret the claim of the applicant.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Andrew Wang, Supervisory Patent Examiner, can be reached at (571) 272-0811.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
21 December 2006

21 December 2006

21 December 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER